

CURRENT LISTING OF CLAIMS

1. (Original) An isolated agent comprising a core peptide selected from the group consisting of Core peptides 5 through 39 and 42 through 55, wherein said agent derepresses an IAP-inhibited caspase.
2. (Original) An isolated agent comprising a structure selected from any of the structures shown in Figure 5, any of the structures shown in Figure 9, any of the structures shown in Figure 10, any of the structures shown in Figure 14B, wherein said agent derepresses an IAP-inhibited caspase.
3. (Original) The agent of claim 1 or 2, wherein said agent derepresses an XIAP-inhibited caspase.
4. (Original) The agent of claim 1 or 2, wherein said agent derepresses an XIAP-inhibited caspase-3.
5. (Original) A pharmaceutical composition comprising the agent of claim 1 or 2 and a pharmaceutically acceptable carrier.
6. (Original) A complex comprising an IAP bound to an agent selected from the group consisting of a core peptide having a sequence set forth in any of Core peptides 4 through 39 and 42 through 55, and an agent having a core structure selected from the group consisting of TPI 759, TPI 882, TPI 914 or TPI 927.
7. (Original) The complex of claim 6, wherein said IAP is selected from the group consisting of XIAP, c-IAP-1, c-IAP-2, and survivin.
8. (Original) A method of derepressing an IAP-inhibited caspase, comprising contacting an IAP-inhibited caspase with an effective amount of an agent to derepress an IAP-inhibited caspase, said agent having a core motif selected from the group consisting of a core peptide having a sequence set forth in any of Core peptides 4 through 39 and 42 through 55, and a core structure selected from the group consisting of TPI 759, TPI 882, TPI 914 or TPI 927.

9. (Original) The method of claim 8, wherein said IAP is selected from the group consisting of XIAP, c-IAP-1, c-IAP-2, and survivin.

10. (Original) The method of claim 8, wherein said caspase is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

11. (Original) The method of claim 8, wherein said contacting is performed *in vitro*.

12. (Original) The method of claim 8, wherein said contacting occurs in a cell.

13. (Original) A method of promoting apoptosis in a cell, comprising contacting a cell with an effective amount of an agent to derepress an IAP-inhibited caspase, said agent having a core motif selected from the group consisting of a core peptide having a sequence set forth in any of Core peptides 4 through 39 and 42 through 55, and a core structure selected from the group consisting of TPI 759, TPI 882, TPI 914 or TPI 927.

14. (Original) The method of claim 13, wherein said cell is a eukaryotic cell.

15. (Original) The method of claim 13, wherein said IAP is selected from the group consisting of XIAP, c-IAP-1, c-IAP-2 and survivin.

16. (Original) The method of claim 13, wherein said caspase is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

17. (Original) A method of reducing the severity of a pathologic condition in an individual, comprising administering to an individual having a pathologic condition characterized by a pathologically reduced level of apoptosis, an effective amount of an agent to derepress an IAP-inhibited caspase, said agent having a core motif selected from the group consisting of a core peptide having a sequence set forth in any of Core peptides 4 through 39 and 42 through 55, and a core structure selected from the group consisting of TPI 759, TPI 882, TPI 914 or TPI 927.

18. (Original) The method of claim 17, wherein said pathologic condition is cancer.

19. (Original) The method of claim 17, wherein said pathologic condition is selected from the group consisting of psoriasis, hyperplasia, an autoimmune disease and restenosis.

20. (Original) The method of claim 17, wherein said IAP is selected from the group consisting of XIAP, c-IAP-1, c-IAP-2 and survivin.

21. (Original) The method of claim 17, wherein said caspase is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

22. (Original) The method of claim 17, further comprising administering a second therapeutic agent.

23. (Original) A method of identifying an agent that derepresses an IAP-inhibited caspase, comprising:

(a) detecting a labeled derepressor of an IAP-inhibited caspase bound to an IAP or caspase, said labeled derepressor of an IAP-inhibited caspase comprising a core motif selected from a core sequence set forth in any of Core peptides 4 through 39 and 42 through 55, or a core structure selected from the group consisting of TPI 759, TPI 882, TPI 914 and TPI 927;

(b) contacting the bound IAP or caspase with a candidate agent, said candidate agent suspected of being able to derepress an IAP-inhibited caspase; and

(c) detecting dissociation of said labeled derepressor of an IAP-inhibited caspase from said IAP or caspase, whereby said candidate agent is identified as an agent that derepresses an IAP-inhibited caspase.

24. (Original) The method of claim 23, wherein the IAP is selected from the group consisting of XIAP, c-IAP-1, c-IAP-2, and survivin.

25. (Original) The method of claim 23, wherein said IAP-inhibited caspase is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

26. (Original) The method of claim 23, wherein said contacting is performed *in vitro*.

27. (Original) The method of claim 23, wherein said contacting occurs in a cell.

28. (Original) An isolated agent comprising a core structure selected from any of the structures shown in Figures 21-24, wherein said agent is selected from TPI 1349-1 to TPI 1349-34, TPI 1396-2, TPI 1396-10, TPI 1396-11, TPI 1396-12, TPI 1396-23, TPI 1396-34, TPI 1396-35, TPI 1396-48, TPI 1396-58, TPI 1391-1 to TPI 1391-36, TPI 1400-1 to TPI 1400-30, TPI 1400-32, TPI 1400-39, TPI 1400-40, TPI 1400-41, TPI 1400-47, TPI 1400-49, TPI 1400-52, TPI 1400-55, and TPI 1400-58, and wherein said agent derepresses an IAP-inhibited caspase.

29. (Original) An isolated agent comprising a core structure selected from any of the structures shown in Figure 34, wherein said agent is selected from TPI 1509-1 to TPI 1509-9 wherein said agent derepresses an IAP-inhibited caspase.

30. (Original) An isolated agent comprising a core structure selected from any of the structures shown in Figure 35, wherein said agent is selected from TPI 1540-6, TPI 1540-7, TPI 1540-11 to TPI 1540-18, TPI 1540-21 to TPI 1540-23, wherein said agent derepresses an IAP-inhibited caspase.

31. (Original) The agent of claim 28, 29 or 30, wherein said agent derepresses an XIAP-inhibited caspase.

32. (Original) The agent of claim 28, 29 or 30, wherein said agent derepresses and XIAP-inhibited caspase-3.

33. (Original) A composition comprising the agent of claim 28, 29 or 30 and a pharmaceutically acceptable carrier.

34. (Original) The method of claim 22, wherein said labeled derepressor binds to a non-SMAC-binding site on said IAP.

35. (Original) The method of claim 33, wherein said labeled derepressor is based on a core structure from the TPI 1332 library.

36. (Original) The method of claim 33, wherein said non-SMAC-binding site on said IAP is a site bound by TPI 1332-69.

37. (Original) A method for identifying an agent that derepresses an IAP-inhibited caspase, comprising:

(a) contacting a BIR2 domain with a candidate agent in the presence of a derepressor of an IAP-inhibited caspase, under conditions wherein said BIR2 domain binds to said derepressor, and

(b) detecting dissociation of said derepressor from said BIR2 domain, whereby the candidate agent is identified as an agent that derepresses an IAP-inhibited caspase, wherein said derepressor is selected from an isolated agent comprising a core structure selected from TPI 1391, TPI 1349, TPI 1396, TPI 1509, TPI 1540, TPI 1400, TPI 792 and TPI 1332, whereby the candidate agent is identified as an agent that derepresses an IAP-inhibited caspase.

38. (Original) A method for identifying an agent that derepresses an IAP-inhibited caspase, comprising:

(a) detecting a labeled derepressor of a BIR domain-inhibited caspase, said derepressor bound to the BIR domain of a BIR domain-caspase complex;

(b) contacting the BIR domain-caspase complex with a candidate agent, the candidate agent suspected of being able to derepress a BIR domain-inhibited caspase, and

(c) detecting dissociation of the labeled derepressor of the BIR domain-inhibited caspase from the complex, wherein said derepressor is selected from an isolated agent comprising a core structure selected from TPI 1391, TPI 1349, TPI 1396, TPI 1509, TPI 1540, TPI 1400, TPI 792 and TPI 1332, whereby the candidate agent is identified as an agent that derepresses an IAP-inhibited caspase.

39. (Original) The method of claim 37 or 38, wherein said agent derepresses an XIAP BIR2 domain-inhibited caspase.

40. (Original) The method of claim 37 or 38, wherein said agent derepresses an XIAP-inhibited caspase-3.

41. (Original) The method of claim 37 or 38, wherein said candidate agent is labeled.

42. (Original) The method of claim 37 or 38, wherein said derepressor is labeled.

43. (Original) A method of derepressing an IAP-inhibited caspase, comprising contacting an IAP-inhibited caspase with an effective amount of an agent to derepress an IAP-inhibited caspase, said agent selected from a core structure selected from TPI 1332, TPI 1396, TPI 1349, TPI 1391, TPI 1400, TPI 792, TPI 1509, and TPI 1540, wherein said agent derepresses said IAP-inhibited caspase.

44. (Original) The method of claim 43, wherein said agent is selected from TPI 1332-1, TPI 1332-3, TPI 1332- 4, TPI 1332- 5, TPI 1332- 11, TPI 1332- 15, TPI 1332- 32, TPI 1332- 36, TPI 1332- 38, TPI 1332- 40, TPI 1332- 41, TPI 1332- 42, TPI 1332- 45, TPI 1332- 47, TPI 1332- 63 to TPI 1332- 69, TPI 1332- 71 to TPI 1332- 73, TPI 1332- 76, TPI 1332- 78, TPI 1332- 81 to TPI 1332- 85, TPI 1332- 87 to TPI 1332- 90, and TPI 1332- 93.

45. (Original) The method of claim 43, wherein said agent is selected from TPI 1349-1 to TPI 1349-34.

46. (Original) The method of claim 43, wherein said agent is selected from TPI 1396-2, TPI 1396-10, TPI 1396-11, TPI 1396-12, TPI 1396-23, TPI 1396-34, TPI 1396-35, TPI 1396-48, and TPI 1396-58.

47. (Original) The method of claim 43, wherein said agent is selected from TPI 1391-1 to TPI 1391-36.

48. (Original) The method of claim 43, wherein said agent is selected from TPI 1400-1 to TPI 1400-30, TPI 1400-32, TPI 1400-39, TPI 1400-40, TPI 1400-41, TPI 1400-47, TPI 1400-49, TPI 1400-52, TPI 1400-55, and TPI 1400-58.

49. (Original) The method of claim 43, wherein said agent is selected from TPI 1509-1 to TPI 1509-9.

50. (Original) The method of claim 43, wherein said agent is selected from TPI 1540-6, TPI 1540-7, TPI 1540-11 to TPI 1540-18, and TPI 1540-21 to TPI 1540-23.

51. (Original) A method of reducing the severity of a pathologic condition in an individual, comprising administering to an individual having a pathologic condition characterized by a pathologically reduced level of apoptosis, an effective amount of an agent to derepress an IAP-inhibited caspase, said agent selected from a core structure selected from TPI 1332, TPI 1396, TPI 1349, TPI 1391, TPI 1400, TPI 792, TPI 1509, and TPI 1540, wherein said agent derepresses said IAP-inhibited caspase.

52. (Original) The method of claim 51, wherein said pathologic condition is cancer.

53. (Original) The method of claim 51, wherein said pathologic condition is selected from the group consisting of psoriasis, hyperplasia, an autoimmune disease and restenosis.

54. (Original) The method of claim 51, wherein said IAP is XIAP.

55. (Original) The method of claim 51, wherein said caspase is selected from the group consisting of caspase-3, caspase-7 and caspase-9.

56. (Original) The method of claim 51, further comprising administering a second therapeutic agent.

57. (Original) The method of claim 51, wherein said agent is selected from TPI 1332-1, TPI 1332-3, TPI 1332-4, TPI 1332-5, TPI 1332-11, TPI 1332-15, TPI 1332-32, TPI 1332-36, TPI 1332-38, TPI 1332-40, TPI 1332-41, TPI 1332-42, TPI 1332-45, TPI 1332-47, TPI 1332-63 to TPI 1332-69, TPI 1332-71 to TPI 1332-73, TPI 1332-76, TPI 1332-78, TPI 1332-81 to TPI 1332-85, TPI 1332-87 to TPI 1332-90, and TPI 1332-93.

58. (Original) The method of claim 51, wherein said agent is selected from TPI 1349-1 to TPI 1349-34.

59. (Original) The method of claim 51, wherein said agent is selected from TPI 1396-2, TPI 1396-10, TPI 1396-11, TPI 1396-12, TPI 1396-23, TPI 1396-34, TPI 1396-35, TPI 1396-48, and TPI 1396-58.

60. (Original) The method of claim 51, wherein said agent is selected from TPI 1391-1 to TPI 1391-36.

61. (Original) The method of claim 51, wherein said agent is selected from TPI 1400-1 to TPI 1400-30, TPI 1400-32, TPI 1400-39, TPI 1400-40, TPI 1400-41, TPI 1400-47, TPI 1400-49, TPI 1400-52, TPI 1400-55, and TPI 1400-58.

62. (Original) The method of claim 51, wherein said agent is selected from TPI 1509-1 to TPI 1509-9.

63. (Original) The method of claim 51, wherein said agent is selected from TPI 1540-6, TPI 1540-7, TPI 1540-11 to TPI 1540-18, and TPI 1540-21 to TPI 1540-23.

64. (Original) A method for treating an individual having cancer, comprising administering to the individual an agent selected from a core structure selected from TPI 1332, TPI 1396, TPI 1349, TPI 1391, TPI 1400, TPI 792, TPI 1509, and TPI 1540, wherein the agent derepresses an IAP inhibited caspase, and an anti-cancer drug, thereby increasing the level of apoptosis to treat the individual.

65. (Original) The method of claim 64, wherein said anti-cancer drug is a chemical compound.

66. (Original) The method of claim 65, wherein said chemical compound is selected from etoposide (VP16), doxorubicin (DOX) and paclitaxel.

67. (Original) The method of claim 64, wherein said anti-cancer drug is a biological compound selected from an antibody, cell and polypeptide.

68. (Original) The method of claim 67, wherein said antibody is selected from an antibody that activates caspase 3 and an antibody that activates caspase 7.